REMARKS/ARGUMENTS

Before responding to each of the Examiner's repeated allegations of unpatentability, applicants would initially note that the Examiner has responded to applicants' reference to the lengthy prosecution history of this case, and their contention that the Examiner has completely disregarded that history, including the notice of allowed subject matter set forth in the official action dated October 25, 2005. The Examiner's response, however, not only fails to recognize the "full faith and credit" required to be applied to that history, but, quite to the contrary, constitutes a thinly veiled attempt to "trash" the previous Examiners' reasoning. The Examiner thus refers to page 4 of the official action of October 25, 2005, stating that the prior Examiner merely stated that the specified claims were allowable due to "evidence of unexpected results," but then asserting that it was unclear to precisely what results the Examiner was referring. Of course, beginning on page 5 of that official action, the prior Examiner actually did go into lengthy detail to explain his position, not only about the nature of those unexpected results and why he accepted them, but also with his respect to his overall reasoning in connection with this application. The M.P.E.P. section referred to by the applicants in their previous response, requiring that great care be exercised in authorizing rejection of a claim which has been deemed allowable, certainly does not suggest that this required degree of care and deference can be met simply by casting aspersions upon the work of a fellow Examiner, particularly where, as here, that Examiner went out of his way to explain his reasoning. There is no doubt here that the present Examiner did not demonstrate the "full faith and credit" required by the M.P.E.P., and presumably that would be an issue in the appeal of this case.

The Examiner does attempt to justify his 180° change of position in this case by relying upon the fact that four different Examiners have handled this application. Indeed, Examiner Berman handled this application from its filing in September of 1997 through the filing of the continuation application in December of 2003. The fact that Examiner Wells was named Examiner on a single official action, and that Examiner Sharareh was Examiner in another official action and during a personal interview does not lessen the requirements for giving credit to the prior Examiners' determinations in this case. Applicants submit that, to the contrary, the lengthy prosecution of this application prior to receipt of an indication of allowance merely indicates that the issues were carefully considered by prior Examiners who ultimately concluded that patentable subject matter was presented herein. To turn that very fact on its head and utilize it as a justification for ignoring both the rules and the M.P.E.P. is simply appropriate.

In any event, and with little anticipation of success, applicants will respond to the latest rejection and establish the following:

1. While there is no statutory justification for the M.P.E.P.'s requirement that all inventors execute an affidavit under Rule 131, applicants have prepared and filed such a declaration herewith, thus eliminating the Reed reference hereagainst;

2. The Examiner has misinterpreted the Bardin reference, particularly in light of Declarations by Dr. Bardin himself, and applicants will establish that Bardin does not teach nor suggest what the Examiner contends; and

3. Each of the other combinations of references, which include Bardin *et al.*, do not establish a *prima facie* case of obviousness.

In view of the above, it is at the very least apparent that the Examiner should consider both the enclosed Declaration and the arguments presented herein, even though the present rejection has been made final. The elimination of Reed *et al.* provides good cause for doing so, since it removes at least two of the rejections being relied upon by the Examiner. Beyond that, it is also respectfully submitted that this response not only reduces the issues presented for purposes of appeal, but in fact establishes the patentable nature of all of the presently pending claims. For all of these reasons, reconsideration and allowance of this application is respectfully solicited.

REED *ET AL.* CAN NO LONGER BE CITED AS A REFERENCE, THUS ELIMINATING TWO OF THE PRINCIPAL REJECTIONS IN THIS CASE

In response to the official action dated June 29, 2006, applicants filed a Declaration by one of the inventors, Dr. Tsong, establishing that applicants had made the present invention prior to the effective date of Reed *et al.* In response, the Examiner cited a section of the M.P.E.P. (§ 1715.04) stating that the declaration must be signed by all of the inventors who contributed to the invention.

While acknowledging the existence of this section of the M.P.E.P., applicants submit that there is no statutory authority for this requirement, and that Rule 131 itself does not specify that all inventors must execute such an oath in order to overcome the reference under this provision. Indeed, the showing of facts required is established in Rule 131(b) and has been complied with, even in the initial Declaration filed in this case. Nevertheless, in order to overcome this objection, applicants have now obtained a new Declaration executed by both inventors in this application, therefore establishing that Reed *et al.* is not a proper reference hereagainst.

Since two of the obviousness rejections in this case rely upon Reed *et al.*, it is clear that these rejections are no longer operative. These rejections include that of claims 1 and 3-16 over Bardin in view of Reed *et al.*, and that of claim 23 over Bardin in view of Reed *et al.*, and further in view of Moo-Young, both under 35 U.S.C. § 103(a). This being the case, it appears that at this point, based solely upon the elimination of Reed *et al.* as a reference hereagainst, claims 7-12 do not appear to stand rejected on the basis of any combination of references at all, and are apparently therefore now in condition for allowance. However, in view of the long and tortuous history of this application, applicants will not presume that this is the case, even though these principal rejections have clearly been eliminated. Applicants will thus now also establish that all of the claims in this application are patentable over the remaining references which have been cited herein.

A FAIR ANALYSIS OF THE BARDIN *ET AL.* REFERENCE ESTABLISHES ITS INSUFFICIENCY

The only reference which is an essential element of every obviousness rejection is this case is Bardin *et al.* This reference has clearly been relied upon as the linchpin for rejection of these claims. Dr. Bardin is a co-worker of the inventors, as well as a Declarant in this case. This critical reliance on Bardin *et al.* is, however, believed to be entirely misplaced in view of the overall nature of this reference and the lack of any real "teaching" of any transdermal product therein. Applicants thus again submit that a fair reading of Bardin *et al.* makes it clear that, at best, it amounts to a teaching in the nature of "wouldn't it be nice if 7MNT could be used in a transdermal patch."

As has been spelled out in the past, Bardin *et al.* is primarily directed to the preparation of non-5α-reducible

androgens and to androgen supplementation therapy using same. This reference thus discusses the significance of replacing the use of testosterone with 7MNT, primarily in terms of the lack of conversion to DHT in the prostate, but it only discloses the use of this drug by means of direct injection. Bardin *et al.* thus sets forth a general disclosure of the amount of the testosterone derivatives which are administered, depending upon "the potency of the compound and the route of administration." The specification of Bardin *et al.* then discusses a general dosage applicable to these drugs, and as has been pointed out on several occasions, the entire specification of Bardin *et al.* does not include a single suggestion, reference or teaching whatsoever of the transdermal administration of any compounds, much less the non-5α-reducible androgens. The sole disclosure of Bardin *et al.* relied upon by the Examiner is that set forth in unsupported claim 4 which states that "the testosterone derivative is administered intramuscularly, subcutaneously or transdermally in an amount of from 5 to 10 μg/kg of body weight." (Emphasis added.) Again, this is the entire disclosure of transdermal application of 7MNT relied upon by the Examiner. Applicants admit that no matter how this disclosure found its way into the claims of the Bardin *et al.* reference, it certainly exists and must be dealt with. On the other hand, however, it must be viewed in light of the overall disclosure of Bardin itself, and the overall nature of that teaching can only be evaluated in view of its relationship to that entire disclosure. In that context, since it refers to "transdermal" only in the context of intramuscular and subcutaneous, it is clear that there is absolutely no teaching of how one could possibly provide a transdermal product of this nature. The entire disclosure clearly amounts to a general thought that such

a product might be nice to have — if one could actually produce it.

Applicants' position with respect to Bardin is not solely based on a contention that this disclosure is nonenabling, although that is clearly the case here. But, beyond that, if one of ordinary skill in this art were to honestly consider Bardin, applicants, as well as Dr. Bardin himself, urge that they could only conclude that this reference to "transdermal" must simply be an error — since there is nothing in Bardin to suggest that such a product would actually work, much less precisely how it could be produced. When the Examiner thus suggests that, even if nonenabling, this reference nevertheless suggests to one of ordinary skill the claimed, highly successful, operative product of the present invention. There is simply no support for this assumption. That amounts to the Examiner concluding that the mere "thought" of applying the drug products of Bardin in a transdermal product is all that is required to obviate the invention of those who, unlike anyone else, were actually able to convert that thought into a useful and highly important commercial product. It that were so, then there actually is no need for the reliance on Bardin at all, since one could surmise that anyone of ordinary skill in this art might have had the desire to produce such a transdermal product. But, that hope alone is submitted to be entirely insufficient to obviate this important invention.

Applicants also submit that the Examiner's refusal to consider the Declaration of Dr. Bardin is inappropriate. Thus, Dr. Bardin has submitted a sworn Declaration, essentially confirming what one of ordinary skill in this art would know from reading the Bardin *et al.* reference; *i.e.*, that at the time the application was filed no work at all had been done on any transdermal applications of any steroid compounds, including the 7MNT disclosed therein. In addition, Dr. Bardin has referred to

claim 4 from his patent, explaining that the overall nature of the disclosure of Bardin *et al.*, and in particular the nature of claim 4 itself, which equates administration "intramuscularly, subcutaneously or transdermally" can at best be said to teach one of ordinary skill that the same amount of the drug itself (namely, from 5 to 10 μg/kg of body weight) should be employed in all three of these cases; *i.e.*, either put into a syringe or into a transdermal product. Certainly, the inventor's own opinion on this is at least that of one of ordinary skill. But even without that opinion, the nature of that disclosure cannot possibly be interpreted otherwise. No other conclusion could be reached from this disclosure, particularly since this language in claim 4 is unsupported by anything else in the specification of Bardin *et al.* As Dr. Bardin explains, when administering these testosterone derivatives either intramuscularly or subcutaneously virtually all of the drug will get into the bloodstream and become bioavailable. Without having even tested any transdermal products containing any of these drugs, however, one would not have any understanding of precisely how bioequivalent amounts of the same drug could be applied in this manner. All that can thus be said is that one would apply the same amount of drug as one applies intramuscularly or subcutaneously (namely, from 5 to 10 μg/kg of body weight) in a transdermal device. Without more disclosure, the Examiner is simply reading the present disclosure into this prior art in order to obviate this invention. However, as Dr. Bardin goes on to note, based on work which was carried out subsequent to the Bardin *et al.* patent, no steroids of which he is aware could provide, in a transdermal product, comparable amounts of drug as would be required if one were operating intramuscularly or subcutaneously. It would be critical to first determine precisely how, or even if, these drugs can be applied

transdermally before one could be said to have been "taught" how to produce such a product as that claimed herein.

Applicants have also submitted the Declaration of Dr. Radlmaier in this case. In that sworn statement, Dr. Radlmaier further confirms the statements of Dr. Bardin, and again concludes that the meager disclosure in claim 4 provides no information whatsoever to one of ordinary skill in this art as to how to actually make any product for the effective transdermal administration of non-5α-reducible, 7α-modified androgens including 7MNT, and in fact does not even teach that such a product could actually be made. Dr. Radlmaier again emphasizes the significant differences between intramuscular and subcutaneous application of a drug as contrasted to the transdermal application of same. Without a true teaching in the art, one would not have the slightest idea whether a particular drug, such as 7MNT, could even work in such an environment, much less how to make it work if that were the case.

These Declarants then went on to specifically discuss the fact that the use of 5 to 10 μg/kg of body weight would be far too low to be useful for the purposes of the present invention. Thus, if one were to actually follow the teachings of Bardin *et al.* and prepare a transdermal product containing from 5 to 10 μg/kg of body weight of 7MNT, the product would be essentially useless. For an average body weight of 70 kg, even at the upper limit of claim 4 (namely, 10 μg/kg), a total of 0.7 mg of the androgen in question, an amount which might be useful if applied intramuscularly or subcutaneously, would clearly be insufficient if placed in a transdermal product. Indeed, the Declarants have established that, based on the now-known total bioavailability of 7MNT, effective treatment of hypergonadal males requires transdermal application of at least from 5 to 10 mg of 7MNT. Thus, the claims in this application

require a sufficient amount of the androgen to deliver between about 400 and about 1600 μg of the androgen in bioavailable form over a 24-hour period. These results are based upon the overall disclosure of the nature of this product, and an understanding of the flux rates and the utility of 7MNT in a transdermal environment, none of which is even suggested by Bardin *et al.*

The Examiner's response is to allege that Bardin *et al.* teaches a transdermal product which somehow actually delivers from 5 to 10 mg/kg of body weight of 7MNT, translating to a dose of 350 to 700 μg for a 70 kg patient. Where does the Examiner extract this disclosure from? Again, the specification of the Bardin *et al.* patent does not refer to any androgen being applied transdermally, nor the amounts required to achieve specific bioavailable amounts of 7MNT therewith. Indeed, the Bardin *et al.* patent does not even disclose that drugs such as 7MNT are actually capable of being delivered transdermally. Claim 4 thus merely treats intramuscular, subcutaneous and transdermal administration in a single brief disclosure therein, stating that the testosterone derivative "is administered" in these manners in amounts of from 5 to 10 μg/kg of body weight. There is no suggestion that the inventors somehow stated in this patent that in order to effectively apply 7MNT by the transdermal route, one needs to actually "administer" far larger amounts of androgen, or any amounts which can effectively apply 5 to 10 μg/kg of body weight of 7MNT in a bioavailable form to the patient. Where does the Examiner suggest that this disclosure arises from? Claim 4 merely states that specific amounts are administered in one of these three manners. The rest of the disclosure is created by the Examiner out of thin air, based upon applicants' disclosure and the knowledge in the art subsequent to the date of the Bardin *et al.* reference. A fair and honest reading of this reference, and the sole disclosure in

claim 4 thereof, cannot possibly amount to a legitimate suggestion of the present invention, or again even that it is possible to delivery drugs such as 7MNT transdermally in the first place. As confirmed by Dr. Bardin, at the time of the Bardin *et al.* patent it was not even known if 7MNT could be applied transdermally at all. Since that was the case, what would the meaning of claim 4 actually be? It would, as applicants have submitted throughout, merely be a "prayer" for a hoped-for result which was clearly unknown or unexpected by these patentees at the time. The Examiner, on the other hand, equates this with amounts actually delivered in bioavailable form, and then states that they overlap the claimed range of the present claims. There is simply no basis for the Examiner's contention in this regard.

The Examiner goes on to assert that a "non-enabling reference may qualify as prior art for the purpose of determining obviousness under § 103." The Examiner thus concludes that Bardin *et al.* provides sufficient motivation to look for references teaching known formulations for transdermal delivery of 7MNT, and then states that upon examining Reed *et al.* one would expect that 7MNT can be formulated in transdermal delivery systems exemplified by Reed *et al.* to deliver the doses taught by Bardin *et al.*

Firstly, the Examiner's broad allegation concerning non-enabling references is not helpful. The fact of the matter is that references must be read in context to determine the true nature of their disclosure, and if they are not enabling, they certainly do not provide the same depth of teaching which one requires for a conclusion of obviousness. Secondly, even accepting the Examiner's suggestion, since Reed *et al.* is no longer a reference hereagainst, a critical element of the Examiner's allegations in this regard now disappears. Thus,

this combination can no longer be relied upon and the Examiner's logic now has no basis in fact or law.

THE EXAMINER'S INHERENCY ARGUMENT IS INAPPROPRIATE

Applicants have previously responded to the Examiner's contention that sections of the M.P.E.P. support the position that, if the prior art teaches the identical chemical structure, the properties applicants disclose and/or claim are necessarily present therein. Applicants had responded by stating that the Examiner was not making an anticipation rejection, and thus was not asserting that the identical compound was being claimed in the prior art. Indeed, that assertion cannot be made as is discussed at length herein. The Examiner, in fact, specifically admits that Bardin *et al.* and Reed *et al.* do not disclose the claimed weight percentage of 7MNT in a transdermal delivery system. It is thus clear that this is not an anticipation rejection, but is clearly based on obviousness. For this reason, applicants had stated that the Examiner's overall references to the M.P.E.P. and case law such as *In re Spada*, 911 F.2d 705,709, 15 U.S.P.Q.2d 1655, 1658 (Fed. Cir. 1990) were inappropriate.

Simply stated, the Examiner's contention that obviousness can be concluded by inherency is insufficient as a matter of law. For example, as explained in *In re Newell*, 891 F.2d 899 (Fed. Cir. 1989):

> A retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in a particular claimed combination. It is well established that in deciding that a novel combination would have been obvious, there must be supporting teaching in the prior art. "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Spormann* 363 F.2d 444, 448 (C.C.P.A. 1966.

Newell, 891 F.2d at 901. (Citations omitted.) *See also In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) ("Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection."; *Kolster Speedsteel AB v. Crucible Inc.*, 793 F.2d 1565, 1576 (Fed. Cir. 1986). "Inherency and obviousness are distinct concepts."

The Examiner's sole support for his contrary position appears to be based upon the citation of *In re Best*, 562 F.2d 1252, 1255, 195 U.S.P.Q. 430, 433 (C.C.P.A. 1977), which the Examiner contends has not been addressed by applicant. This case, however, clearly does not negate the subsequent decisions of the C.C.P.A. and Federal Circuit. Indeed, in the *Best* case, the court specifically stated that:

> Whether the rejection is based upon "inherency" under 35 U.S.C. § 102, on "*prima facie* obviousness" under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products.

The court itself thus clearly distinguished between inherency under § 102 and *prima facie* obviousness under § 103. There is no reference to inherency under § 103, and indeed, as set forth above, those arguments are entirely separate.

The fact of the matter is that the Examiner is not relying and could not truly rely upon an "inherency" argument in this case. While the Examiner may be contending that flux properties are inherent properties of transdermal formulations, there is no allegation that the prior art specifically teaches the claimed formulations thereof, and therefore there is no prior art formulation which could be said to "inherently" include applicants' claimed product, including the specified amounts of 7MNT therein. Indeed, applicants do not claim the flux properties which the Examiner contends are "inherent" in

the art, but only establish that, having determined the nature of these properties for the first time, applicants were then able to devise the present invention based thereon. The Examiner cannot legitimately contend that there are "known products" in the prior art which inherently possess the properties and requirements of the claims herein. That simply is not the case.

The fact of the matter is that, as a legal matter, the Examiner's contention that "inherent properties are present in known products as well as products rendered obvious by the prior art" is meaningless in reference to the present rejections, and is, in fact, an incorrect assertion. Applicants are not claiming an inherent property, but are merely relying upon that property to establish the patentability of their claimed invention of a product which is capable of delivering a specified bioavailable dosage of 7MNT via the transdermal route which has not been possible hereinbefore. The prior art simply does not teach the presently claimed invention and does not render it obvious by means of inherency, which is an inappropriate standard in the first instance.

THE COMBINATION OF JAIN *ET AL.*
WITH BARDIN *ET AL.* DOES NOT OVERCOME
THE DEFICIENCIES OF THE BARDIN *ET AL.* REFERENCE

As has already been pointed out by applicants, the Jain *et al.* reference was first employed as a basis for rejecting claims in this application on July 9, 1999. Applicants pointed out at that time that references such as Jain *et al.* failed to identify even non-5α-reducible androgens, much less the 7α-modified androgens such as 7MNT to which the present claims are directed. The mere recitation of broad classes of androgens was not only established as being non-anticipatory, but this patent was said to have a broad enough disclosure so that thousands of steroid-based compositions, including but not

limited to androgens, were set forth therein. Applicants thus pointed out that a generic recitation which reads on so many compounds cannot possibly "disclose" and therefore anticipate each and every species contained within its scope, citing *In re Rushig*, 379 F.2d 990 (C.C.P.A. 1967). It was also pointed out that Jain *et al.* identifies as its preferred androgens testosterone and esters thereof (*see* col. 5, ln. 7 thereof). Testosterone, however, is 5α-reducible and therefore represents the antithesis of the present invention. Indeed, the very comparative data which is set forth in the present specification and which was highlighted throughout the early stages of the prosecution of this application clearly distinguish over references teaching testosterone, such as Jain *et al.*

In any event, reference to Jain *et al.* was withdrawn as early as 2001, and has only now been reinserted after a five-year hiatus. Nevertheless, Jain *et al.* now returns on the very same basis that was the case so many years ago; namely, as a basis for an assertion that claims 1, 3-6, and 13-16 are obvious over Jain *et al.* in view of Bardin *et al.*

The fact is that, totally aside from the fact that Jain *et al.* does not disclose the particular steroids or class of steroids to which the present claims are directed, the combination of Jain *et al.* and Bardin *et al.*, if Bardin *et al.* is properly construed in the manner discussed above, neither teaches nor suggests the present invention. There is simply no basis for concluding that one of ordinary skill in the art would be motivated to combine these references to overcome the deficiencies of Bardin *et al.* with respect to a transdermal product which is even capable of delivering the specific amount of 7MNT required by these claims. It is clear that this is a hindsight reconstruction of the prior art, and that there is no reason whatsoever for one to combine these references when they are not even directed to the same products. Even the Examiner's

own reasoning for combining these references, stating that it would be obvious to incorporate the 7MNT of Bardin *et al.* into the transdermal delivery systems of Jain *et al.*, requires one to then engage in the further exercise of allegedly "optimizing" the amount of 7MNT in the system in order to achieve any useful results from that combination of references. This is precisely the point, however. There is no basis for presuming that this is even a mere "optimization." The "product" presumably disclosed in Bardin *et al.*, if any such product is actually disclosed, simply would not work. To then combine this failed disclosure with a reference which does not even teach the same 7MNT to which the present claims are directed, to somehow arrive at a useful product, is simply not warranted. Indeed, the amounts of 7MNT required in order to obtain the claimed bioequivalent product of the present claims is not even suggested in Jain *et al.* to begin with.

THE REJECTIONS OF CLAIM 23 CAN NO LONGER STAND.

Claim 23 has been alternatively rejected as being obvious over Badin *et al.* in view of Reed *et al.* and further in view of Moo-Young *et al.*, or over Jain *et al.* in view of Bardin *et al.* and further in view of Moo-Young *et al.*

Firstly, the initial rejection relying upon Reed *et al.* is no longer applicable, as discussed above. Applicants have already set forth their position with respect to the inadequacies of the Bardin *et al.* reference, and those are merely reiterated at this point. The mere allegation that Moo-Young teaches the acetate salt of the claimed compound clearly cannot be said to overcome the deficiencies of these references, particularly in view of the inappropriate citation of Reed *et al.*

As for the second combination of references, applicants have also set forth their detailed position with

respect to the inadequacies of Bardin *et al.*, as well as Jain *et al.* Once again, the mere recitation of Moo-Young for the purpose of disclosing the acetate salt does not overcome any of these inadequacies. It is therefore respectfully submitted that, like the other claims in this application, claim 23 is also in condition for allowance.

CONCLUSIONS

Applicants respectfully submit that with the elimination of Reed *et al.* as a reference hereagainst, this application includes patentable subject matter, at the very least to the extent that the present claims include claims which are no longer the subject of any prior art rejection. Beyond that, however, and in view of the utter inadequacies of the disclosure in Bardin *et al.* with respect to any useful transdermal products, and in particular with respect to the claimed products hereof, it is respectfully submitted that all of the rejections in this case simply do not pass muster when objectively analyzed in view of the history of this application, the various Declarations which have been submitted herein, and applicants' arguments thereover. It is therefore respectfully requested that the Examiner reconsider the rejection of these claims, and that in doing so it will be appreciated that the claims in this application clearly do possess the requisite novelty, utility and unobviousness to warrant their immediate allowance, which action is respectfully solicited.

It is finally noted that the Examiner has also entered a provisional double-patenting rejection, However, since this is a provisional rejection, and since the claims in Application No. 10/741,207 have not been allowed, this rejection does not warrant a detailed response at this time.

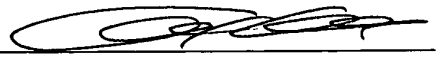
Once again, however, if the Examiner does not agree with applicants' assertions with regard to the patentability of

these claims, it is respectfully requested that the Examiner telephone applicants' attorney at 908-654-5000 in order to overcome any further objections the Examiner may have to the ultimate allowance of these claims.

Finally, if there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: April 5, 2007

Respectfully submitted,

By 

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